Editorial

Cognitive and behavioural outcomes: are they impaired in children without cerebral palsy following neonatal hypoxic-ischaemic encephalopathy?

Ela Chakkarapani,
Email Ela.chakkarapani@bristol.ac.uk
Translational Health Sciences, University of Bristol, St Michael's Hospital, University Hospitals Bristol NHS Trust, Bristol, UK

Schreglmann and colleagues report in this issue of Acta Paediatrica a systematic review of long-term cognitive and behavioural outcomes of neonatal hypoxic ischaemic encephalopathy (HIE) in children without cerebral palsy (CP).[1]Their research question was: In children, who had the "exposure" of neonatal HIE and did not develop CP, what are the cognitive and behavioural outcomes at 4 to 19 years of age?

The authors define neonatal HIE as encephalopathy secondary to perinatal asphyxia including metabolic acidosis within 60 minutes of age, low Apgar scores at 5 minutes or beyond, acute perinatal event and need for prolonged resuscitation or ventilation in infants born >35 weeks gestation. The primary outcomes of general or specific cognitive abilities and behaviour were required to be assessed using standardised psychometric test or questionnaire. Randomised or nonrandomised controlled trials and observational studies were included. Study selection was independently carried out by two
authors, and the quality was assessed using the Newcastle-Ottawa scale. A total of seven eligible studies (5 cohort and 2 case–
control studies) were included. Given the heterogeneity of the case definition in the selected studies, authors were able to conduct meta-analysis only on the effect of moderate HIE on full-scale IQ in children without CP compared to control children who did not have HIE. Rest of the outcome data were summarised as a narrative synthesis. General cognitive abilities were described as the mean difference in IQ between children without CP surviving HIE and controls, and the proportion of children with IQ > 1SD below the population norm. The psychometric tests used were WPPSI-R, WISC-III, NEPSY II and
BAS-II. Specific cognitive abilities included the description of performance on the subscales of psychometric tests. Behavioural outcomes included a summary of the results of the included studies.

Therapeutic hypothermia is the current standard treatment for HIE. Authors set out to determine the effect of exposures 'therapeutic hypothermia' and 'HIE' on the cognitive and behavioural outcomes of children without CP aged between four and

19 years. Their protocol had to be amended to limit the exposure to ‘HIE’ and include only the studies that published cognitive and behavioural outcomes of children who had HIE and did not develop cerebral palsy. Although
two major randomised controlled trials of therapeutic hypothermia (TOBY and NICHD) published the school-age cognitive and behavioural outcomes of children who were either cooled or noncooled[2, 3], only NICHD trial published data for children without CP and therefore data from TOBY study was excluded.[4]

From the included cohort studies, there were 180 noncooled children, and from the included case–control studies there were 119 noncooled children aged between four and 19 years born between 1985 and 2008. Whilst 153/180 (85%) children were assessed in the cohort studies, outcome data was available for all children in the case–control studies. Fifty-three children who underwent therapeutic hypothermia from the NICHD trial were included in this review. One of the main issues was the marked variability in the case definition between the studies which averted a full meta-analyses of the
data.

Outcomes of children without CP who were not cooled for HIE

The review shows that the mean difference in IQ between the children without CP surviving HIE and the controls varied between studies depending on the severity of encephalopathy. Mean IQ in cases compared to controls was 10 points lower in mild encephalopathy group, the difference was non-significant in
moderate encephalopathy group in the meta-analysis but was 17 points lower in one of the studies included in the meta-analysis and 11 points lower in severe encephalopathy group. The proportion of children with IQ > 1 SD below the population mean ranged between 6% and 63% depending on the severity of encephalopathy of the cohort and the robustness of definition of encephalopathy secondary to perinatal asphyxia. Whilst the proportion of children with IQ > 1SD below the population mean was between 25% and 36% in studies with a robust definition of HIE; it was between 6% and 63% with less robust definitions of HIE.

Two studies contributed to the authors’ summary of the specific cognitive abilities. Attention and executive function, and memory and learning domain scores were significantly lower in the moderate encephalopathy group compared to the mild encephalopathy group, and severe encephalopathy group compared to the moderate encephalopathy group. Compared to controls, severe encephalopathy group had a lower score in several domains of psychometric
tests including attention and executive function, language, visuospatial, memory and learning, memory for names and narrative memory. Children who had moderate

encephalopathy compared to controls had lower scores in language and sensorimotor domain, narrative memory and sensory repetition.

Four studies contributed data for the behavioural outcome. Behavioural outcomes were derived from questionnaires completed by parents (SDQ, CBCL, Connors-10 item scale, ADHD rating scale IV, Asperger syndrome screening questionnaire) or teachers (SDQ). In children who had severe encephalopathy, parents reported higher rates of hyperactivity and impaired behavioural score, and teachers reported more emotional, hyperactivity and reduced prosocial
score. Nearly 27.8% of children with moderate encephalopathy had internalising problems compared to 7.3% of children who had mild encephalopathy. However, a Dutch study did not corroborate this finding. Higher scores were reported in the inattention subscale of the ADHD rating scale and Asperger syndrome screening questionnaire in 28 children with HIE compared to 15 siblings.

Outcomes of children without CP who were cooled for HIE

Major clinical trials of therapeutic hypothermia for HIE did not publish the spectrum of cognitive outcomes in children without CP. Data from the only study included in the systematic review showed that out of 53 cooled children, 43% had an IQ<84. Recently published case–control studies from contemporary cooling cohorts have shown that survivors of HIE aged six to eight years without CP compared to age, sex and social class matched controls have significantly lower IQ, verbal comprehension, perceptual reasoning, working memory and processing speed. Parents reported higher emotional and
behavioural difficulties. These cognitive impairments are reflected by the significantly higher need for additional support at school in the case group. [5] Case children with lower cognitive scores had lower motor performance scores on movement assessment battery for children—second edition.[6] Furthermore, school-aged children cooled for HIE and did not have CP have lower attention
and visuospatial function compared to age, sex and social class matched controls. [7]

Given the complexity of the various definitions used in the studies to identify children with HIE and a wide age range when the cognitive assessments were conducted in the studies included in the systematic review, authors assessed the quality of the studies and synthesised the data for the primary outcome. Understandably, a full meta-analysis was not undertaken. Since 2010, all infants with HIE are offered therapeutic hypothermia in developed countries.
Therefore, the relevance of these data for the clinicians and the parents is very limited in the developed world. The difference in the population and the care settings preclude generalising these data to the low- and middle-income countries. Regarding

data from infants who underwent therapeutic hypothermia, it is unfortunate that authors had data only from the CoolCap trial. Perhaps more detailed school-age outcome data from the TOBY and NICHD trial would have made this review more relevant to the developed world.
This restricted the sample size of cooled children without CP to only 53 and limited the outcome to only IQ scores. This review presented the data predominantly on non-cooled children who had HIE compared to control children or population norm. The effect of therapeutic hypothermia on the full spectrum of cognitive development is unknown. We do not know how the children differed in the spectrum of cognitive and behavioural development, when infants with HIE treated with therapeutic hypothermia are compared to the untreated group. Lack of consistent definition of the severity of encephalopathy, and lack of data on the evidence of brain injuries on neonatal neuroimaging, and the unavailability of information on the impact of social class on the outcome in the studies included in the systematic review makes it challenging to attribute the cognitive and behavioural outcome exclusively to being exposed to HIE. The review concludes with the message of the need for long-term follow-up of children following HIE. Given the pattern of cognitive difficulties in children without CP cooled for HIE in the recent studies of contemporary cooling cohorts, this conclusion holds even after therapeutic hypothermia. To utilise the limited resources appropriately, we are yet to identify the children cooled for HIE at risk of developing later cognitive impairments in the absence of CP.

Conflict of interest
The author has no conflict of interests.

References
1 Schreglmann M, Ground A, Vollmer B, Johnson MJ. Systematic Review: Long-term cognitive and behavioural outcomes of neonatal hypoxic-ischaemic encephalopathy in children without cerebral palsy. Acta Paediatr 2019. https://doi.org/10.1111/apa.14821.

2 Azzopardi D, Strohm B, Marlow N, Brocklehurst P, Deierl A, Eddama O, et al. Effects of hypothermia for perinatal asphyxia on childhood outcomes. N Engl J Med 2014; 371: 140–9.

3 Shankaran S, Pappas A, McDonald SA, Vohr BR, Hintz SR, Yolton K, et al. Childhood outcomes after hypothermia for neonatal encephalopathy. N Engl J Med 2012; 366: 2085–92.

4 Pappas A, Shankaran S, McDonald SA, Vohr BR, Hintz SR, Ehrenkranz RA, et al. Cognitive outcomes after neonatal encephalopathy. Pediatrics 2015; 135: e624–34.

5 Lee-Kelland R, Jary S, Tonks J, Cowan FM, Thoresen M, Chakkarapani E. School-age outcomes of children without cerebral palsy cooled for neonatal hypoxic-ischaemic encephalopathy in 2008–2010. Arch Dis Child Fetal Neonatal Ed 2019.

6 Jary S, Lee-Kelland R, Tonks J, Cowan FM, Thoresen M, Chakkarapani E. Motor performance and cognitive correlates in children cooled for neonatal encephalopathy without cerebral palsy at school age. Acta Paediatr 2019.

7 Tonks J, Cloke G, Lee-Kelland R, Jary S, Thoresen M, Cowan FM, et al. Attention and visuo-spatial function in children without cerebral palsy who were cooled for neonatal encephalopathy: a case-control study. Brain Inj 2019; 1–5.